ORIGINAL ARTICLE

Customised birthweight standards accurately predict perinatal morbidity

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Objective: Fetal growth restriction is associated with adverse perinatal outcome but is often not recognised antenatally, and low birthweight centiles based on population norms are used as a proxy instead. This study compared the association between neonatal morbidity and fetal growth status at birth as determined by customised birthweight centiles and currently used centiles based on population standards.
Design: Retrospective cohort study.
Setting: Referral hospital, Barcelona, Spain.
Patients: A cohort of 13 661 non-malformed singleton deliveries.
Interventions: Both population-based and customised standards for birth weight were applied to the study cohort. Customised weight centiles were calculated by adjusting for maternal height, booking weight, parity, ethnic origin, gestational age at delivery and fetal sex.
Main outcome measures: Newborn morbidity and perinatal death.
Results: The association between smallness for gestational age (SGA) and perinatal morbidity was stronger when birthweight limits were customised, and resulted in an additional 4.1% (n = 565) neonates being classified as SGA. Compared with non-SGA neonates, this newly identified group had an increased risk of perinatal mortality (OR 3.2; 95% CI 1.6 to 6.2), neurological morbidity (OR 3.2; 95% CI 1.7 to 6.1) and non-neurological morbidity (OR 8; 95% CI 4.8 to 13.6).
Conclusion: Customised standards improve the prediction of adverse neonatal outcome. The association between SGA and adverse outcome is independent of the gestational age at delivery.

Growth restriction is considered to be a major contributor to perinatal morbidity and mortality, being responsible for 50% of perinatal deaths occurring preterm and 20% at term.[1] In addition, growth restriction is associated with intrapartum distress and metabolic acidosis, which, in turn, contribute to hypoxic encephalopathy and cerebral palsy.[2] Furthermore, there is increasing evidence of association between fetal growth restriction and infant death[3] and metabolic syndrome in adulthood.[4]

The failure to identify small for gestational age (SGA) fetuses has been identified as an important cause of perinatal morbidity, with a fourfold risk for adverse perinatal outcome.[5] Traditionally, birth weight has been classified using population-based sex-adjusted centiles with a baby being SGA if the birth weight is below the tenth centile, using SGA as a proxy for growth restriction. However, this definition identifies a heterogeneous group that consists of neonates with growth restriction as well as constitutionally and otherwise healthy SGA babies. Whereas growth-restricted babies are those who do not reach their genetic growth potential, healthy SGA babies are considered to represent one end of the normal spectrum of size. This differentiation is not straightforward because fetal growth is markedly influenced by many fetal and maternal physiological factors apart from the length of gestation, such as sex, parity, maternal height and weight, and ethnicity.[6] The use of customised birthweight standards that take these factors into account has been shown to improve the identification of SGA.[7 8]

The present study aimed to analyse the risk of neonatal morbidity in neonates classified as SGA and non-SGA using customised and population-based centiles.

METHODS

The dataset used for this study was anonymised, and the local ethics committee approved the study design.

Study population

We conducted this study at a referral university hospital in Barcelona (Spain) covering an inner-city area at sea level with about a million inhabitants. We created a retrospective cohort from all deliveries attended in our maternity unit between 1 January 2001 and 30 June 2005 by extracting prospectively recorded data, including demographic and clinical data, from the hospital database. Our inclusion criteria were singleton pregnancy delivered after 24 completed weeks and absence of congenital malformations (including chromosomal abnormalities).

A total of 15 464 deliveries attended during the study period fulfilled the inclusion criteria. The customised weight centile could not be calculated for 1803 babies because of missing data (maternal ethnicity (n = 124), maternal height or weight (n = 1716), parity (n = 2), early second-trimester corrected gestational age at delivery (n = 22), and neonatal weight (n = 20) or sex (n = 2)) and these were therefore excluded from the study. A large proportion of cases with missing data (863/1803) were high risk in-utero transfers from other hospitals. The remaining 13 661 deliveries formed the population for the current analysis.

Abbreviations: NICU, neonatal intensive care unit; SGA, small for gestational age

Table 1 Characteristics of the neonates included in the present study. Values are mean (SD) or n (%) as appropriate

Nulliparity	8026 (58.8)
Maternal age	30.3 (5.4)
Body mass index	23.4 (4.3)
Smoking at booking	
No smoking	10 640 (77.9)
1–9 cigarettes/day	1773 (13)
10–19 cigarettes/day	912 (6.7)
>19 cigarettes/day	336 (2.5)
Low socioeconomic level*	2683 (19.6)
Ethnic origin	
White-European	10 101 (73.9)
Moroccan	60 (0.4)
South-East Asian	626 (4.6)
Central African	316 (2.3)
South-American	2490 (18.2)
Other	68 (0.5)
Gestational age at delivery (days)	278.6 (14.4) median 280
Birthweight	3219 (550)
Neonatal intensive care unit admission	387 (2.8)

*Routine occupations, long-term unemployment or never worked.

Definitions

We assessed perinatal outcome using the following criteria:

- preeclampsia (blood pressure of at least 140/90 mm Hg on two occasions at least four hours apart with >0.3 g of urine protein every 24 hours);
- elective caesarean section before the onset of labour;
- caesarean section during labour due to fetal distress (sustained fetal bradycardia or non-reassuring pattern with fetal scalp pH <7.20);
- length of stay in the neonatal intensive care unit (NICU; days);
- five-minute Apgar score <7;
- metabolic acidosis (umbilical artery pH at birth <7.10 and base excess >12 mEq/l);
- neonatal hypoglycaemia (requiring intravenous glucose therapy to maintain capillary glycaemia >2.8 mmol/l (50 mg/dl));
- stillbirth (>24 completed weeks);
- neonatal death (0–28 days).

Composite neurological morbidity was defined as the presence of any of the following: seizures,[9] intraventricular haemorrhage >grade II,[10] periventricular leucomalacia,[11] hypoxic-ischaemic encephalopathy,[9] and abnormal neonatal electroencephalogram.[9] Prolonged stay in the NICU was defined as stay >10 days. Composite non-neurological morbidity was defined as the presence of any of the following: prolonged NICU stay without any of the conditions included in neurological morbidity (see above), necrotising enterocolitis,[12] and acute renal failure (serum creatinine greater than 132.6 μmol/l (1.5 mg/dl) or cardiac failure (requiring ionotropic agents).

We defined SGA as a birth weight below the tenth centile according to customised[13] and population criteria.[14] Briefly, customised centiles were calculated for each fetus according to the method described by Gardosi *et al*.[15] The optimal birth weight at 40 weeks was modelled by means of a linear regression model that takes into account maternal ethnic origin, maternal height and booking weight, parity, gestational age at delivery (corrected by early second trimester ultrasound) and fetal sex. Smoking was included in the model but the prediction of optimal fetal weight was made assuming that the women were non-smokers. We used Hadlock's formula,[16] a model that predicts fetal weight for gestational age, to derive the individually optimal fetal weight. The limits of fetal weight were calculated from the standard deviation of the regression model ($\pm 1.28 \times$ coefficient of variation).

The neonates were classified into one of the following groups using the tenth centile:

- Non-SGA according to both population (adjusted by sex and gestational age at delivery)[14] and customised centiles;
- SGA according to population but not customised centiles (SGA population only);
- SGA according to customised but not population centiles (SGA customised only);
- SGA according to both definitions (SGA both).

Statistical analysis

We analysed the qualitative and continuous variables using Pearson-χ^2 or exact Fisher's text (if any expected frequency <5) and one-way analysis of variance tests, respectively. Odds ratios (ORs) and their 95% asymptotic confidence intervals for outcome variables were calculated with the non-SGA group as the reference category. The odds ratios for adverse outcome were adjusted for the gestational age at delivery by means of logistic regression. We used SPSS (version 11.5) for the statistical analysis.

Table 2 Maternal and neonatal characteristics by SGA group. Values are mean (SD) or n (%) as appropriate

	Non-SGA both N=11 586	SGA population only N=204	SGA customised only N=565	SGA both N=1306	p Value	
					Intermediate groups‡	All groups
Nulliparity	6757 (58.3)	166 (81.4)	254 (45)	849 (65)	<0.001*	<0.001*
Body mass index	23.4 (4.2)	21.1 (2.7)	24.9 (5.2)	23.2 (4.2)	<0.001†	<0.001†
Maternal age	30.3 (5.4)	29.6 (5.6)	30.9 (5.2)	30.5 (5.3)	0.02†	0.03†
Non-smoking	9280 (80.1)	134 (65.7)	402 (71.2)	824 (63.1)	0.14*	<0.001*
Low socioeconomic group	2266 (19.6)	39 (19.1)	128 (22.7)	250 (19.1)	0.29*	0.31*
White-European	8475 (73.1)	178 (87.3)	403 (71.3)	1045 (80)	<0.001*	<0.001*
Preeclampsia	195 (1.7)	10 (4.9)	41 (7.3)	75 (5.7)	0.25*	<0.001*
Gestational age at delivery	39.9 (1.9)	39.5 (1.4)	39.3 (3.4)	39.4 (2.5)	0.29†	<0.001†
Delivery <37 weeks	642 (5.5)	2 (1)	111 (19.6)	119 (9.1)	<0.001*	<0.001*
Birth weight	3343 (461)	2700 (204)	2662 (589)	2441 (457)	0.38†	<0.001†

SGA, small for gestational age.
*Pearson-χ^2; †One-way analysis of variance.
‡Between SGA population only and SGA customised only.

Table 3 Perinatal outcome by study group. Values are n (%)

	Non-SGA both	SGA population only	SGA customised only	SGA both	p Value: Intermediate groups	p Value: All groups
Elective CS‡	679 (5.9)	20 (9.9)	47 (8.5)	141 (10.9)	0.54*	<0.001*
Emergent CS for distress¶	304 (26)	6 (3)	24 (4.4)	84 (6.6)	0.4*	<0.001*
Metabolic acidosis§	54 (0.5)	1 (0.5)	9 (1.7)	19 (1.5)	0.3†	<0.001*
Five-minute Apgar <7‡	71 (0.6)	2 (1)	4 (0.7)	17 (1.3)	0.66†	0.035*
Perinatal death	65 (0.6)	2 (1)	10 (1.8)	22 (1.7)	0.74†	<0.001*
OR (95% CI)	–	1.8 (0.4 to 7.2)	3.2 (1.6 to 6.2)	3 (1.9 to 4.9)		
Stillborns	51 (0.4)	2 (1)	10 (1.8)	17 (1.3)	0.74†	<0.001*
Neonatal death‡	14 (0.1)	0 (0)	0 (0)	5 (0.4)	–	0.071*
Neurological morbidity‡	72 (0.6)	2 (1)	11 (2)	17 (1.3)	0.53†	<0.001*
OR (95% CI)		1.6 (0.4 to 6.5)	3.2 (1.7 to 6.1)	2.1 (1.3 to 3.6)		
Seizures‡	20 (0.2)	1 (0.5)	2 (0.4)	5 (0.4)	1†	0.25*
Intraventricular haemorrhage‡	13 (0.1)	1 (0.5)	1 (0.2)	6 (0.5)	0.46†	0.012*
Periventricular leucomalacia‡	3 (0)	0 (0)	1 (0.2)	0 (0)	1†	0.2*
Hypoxic-ischaemic encephalopathy‡	37 (0.3)	0 (0)	2 (0.4)	8 (0.6)	1†	0.29*
Abnormal electroencephalogram‡	45 (0.4)	1 (0.5)	6 (1.1)	7 (0.5)	0.68†	0.1*
Non-neurological morbidity‡	53 (0.5)	1 (0.5)	20 (3.6)	17 (1.3)	0.02*	<0.001*
OR (95% CI)	–	1.1 (0.1 to 7.8)	8 (4.8 to 13.6)	2.9 (1.7 to 5)		
Prolonged NICU stay‡	46 (0.4)	1 (0.5)	17 (3.1)	16 (1.2)	0.05†	<0.001*
Hypoglycaemia‡	112 (1)	0 (0)	14 (2.5)	42 (3.3)	0.03†	<0.001*
Necrotising enterocolitis‡	4 (0)	0 (0)	1 (0.2)	2 (0.2)	1†	0.16*
Acute renal or cardiac failure‡	13 (0.1)	0 (0)	2 (0.4)	3 (0.2)	1†	0.29*

CS, caesarean section; NICU, neonatal intensive care unit; OR, odds ratio; SGA, small for gestational age.
*Pearson-χ^2; †exact Fisher's test.
‡Stillborns excluded; ¶Stillborns and cases with elective caesarean section excluded; §Stillborns and cases with unavailable umbilical cord sample at birth excluded (n = 528).

RESULTS

The final sample of 13 661 excluded the 1803 cases with one or more missing data items, many of which were transfers from other hospitals. The rates of stillbirth and neonatal deaths were higher among the excluded than the included cases (stillbirth 1.3% *v* 0.6%, p = 0.001; death: 0.5% *v* 0.1%, p<0.001, respectively). Table 1 shows the characteristics of the final study population.

According to population-based centiles, 11.1% (1510/13 661) neonates were SGA, whereas according to customised criteria 13.7% (1871/13 661) were SGA. On categorisation into the study groups, 565 (4.1%) were SGA customised only, 204 (1.5%) were SGA population only and 1306 (9.6%) were SGA by both definitions. The remaining 11 586 (84.8%) were non-SGA by both definitions. Table 2 shows the maternal and neonatal characteristics for each of the four study groups. In summary, women in the SGA population only group were thinner and smaller. Furthermore, this group had a lower frequency of prematurity.

Table 3 provides details of perinatal outcome by study group. Remarkably, perinatal outcome in the SGA population only and non-SGA according both defintions groups did not differ significantly. On the other hand, instances of adverse outcome were more common among the SGA customised only and SGA by either definition groups. The odds ratios for neurological and non-neurological morbidity adjusted for the gestational age at delivery were 1.62 (95% CI 1.02 to 2.57) and 2.1 (95% CI 1.23 to 3.57), respectively, for the customised SGA cases, and 1.39 (95% CI 0.81 to 2.35) and 1.5 (95% CI 0.7 to 2.9) for population SGA cases.

DISCUSSION

This study provides evidence that customised assessment of fetal growth status at birth improves the prediction of adverse perinatal outcome. Even though 30% (565/1871) of the customised SGA babies in our study would not have been identified using population centiles, the SGA customised only group accounted for a large proportion of stillborn babies (13%), as well as neurological (11%) and non-neurological (22%) morbidity. In fact, the risk of stillbirth and morbidity was higher in this group than in the SGA by both definitions group. This is in line with the results of the Swedish population-based study,[17] in which the rates of stillbirth, neonatal death and five-minute Apgar score <4 were also highest in this subgroup. We speculate that this is because the definition of SGA according to population standards does not identify most SGA premature neonates. This accounts for our finding of a higher proportion of premature deliveries in the SGA customised only group than in the SGA by both definitions group, which has also been previously reported.[18] The reason why population standards do not accurately detect growth restriction may be because these standards are constructed from a population that includes,

What is already known on this topic

- Fetal growth restriction is associated with adverse perinatal outcome, mainly in preterm neonates, and is often not recognised antenatally.
- Use of customised standards improves the prediction of abnormal 5-min Apgar score, need for neonatal resuscitation, admission to the intensive care unit and perinatal death.

What this study adds

- Use of customised standards improves the prediction of adverse neonatal outcomes.
- This association is independent of the gestational age at delivery.

mainly among preterm babies, a large proportion of non-identified growth-restricted fetuses, thus artifactually lowering the normal ranges for this period.[19]

In the present study, 1.5% of births were SGA according to population standards only. As table 2 shows, the mothers of these babies tended to be smaller and thinner and were more likely to be primiparae. Hence, this subgroup could be considered as constitutionally and otherwise non-pathologically SGA. We found that risks for perinatal mortality and morbidity in this group were not significantly different from the non-SGA by both definitions group. This may have been because of low power in this subgroup associated with the relatively infrequent incidence of adverse outcomes. However, other, larger studies[17 18 20] have found that neonates who are SGA according to population only standards have a similar risk for adverse perinatal outcome as non-SGA neonates.

Prematurity fulfilled the classic criteria to be considered a confounding factor in the association between SGA and neonatal morbidity. On the one hand, prematurity is clearly associated with adverse neonatal outcome, even in normally grown neonates. On the other hand, there is extensive evidence of the association between growth restriction and prematurity.[21] Analysis of large datasets has shown that fetal growth restriction is a strong factor that independently accounts for a large aetiological fraction of prematurity.[22] Hence, the higher the prevalence of SGA among premature babies yielded by an SGA definition, the more likely the confounding effect of prematurity. Therefore, it could be argued that customised standards for SGA better predict adverse outcome only because they identify more premature babies being SGA than population standards. However, the present study shows that even after adjusting for gestational age at delivery, customised SGA remains an important risk factor for neonatal morbidity.

As in other hospital-based studies,[20] and in contrast with population-based series,[17] we found the rate of stillborns and perinatal deaths was higher among the excluded cases, which may have led to a selection bias. However, most excluded cases in our study were high-risk transfers. Therefore we speculate that had these data been included, we would have found a higher proportion of SGA fetuses and adverse perinatal outcome. As our aim was to compare two definitions of SGA and each neonate was its own control, this selection bias most probably did not affect the differences between the two methods.

Our results show that customised standards improve the prediction of adverse neonatal outcome and, therefore, the definition of SGA. The association between customised SGA and adverse outcome is independent of the gestational age at delivery. In conclusion, the current study provides further evidence to support the use of customised standards to assess birth weight. More studies are required to assess the prospective use of customised standards.

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